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Review Article

Polymyositis-dermatomyositis: a clinical review

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Polymyositis (PM) and dermatomyositis (DM) are characterized by chronic inflammation of skeletal muscle and are manifested, in their classic presentation, by proximal muscle weakness accompanied by elevations of the serum creatine kinase (CK) typical electromyography (EMG) changes with polyphasic potentials and muscle biopsy findings of a necrotizing, inflammatory process.[1]

DM is distinguished from PM by a typical rash, usually red, scaly and plaque-like, over the knuckles, wrists, elbows, knees and ankle malleoli and violaceous lesions in the periorbital and trunk area.[2] Most authors, however, consider DM and PM together since the disease course and muscle lesions are the same, whether skin lesions are present or not.[3]

These diseases are of unknown aetiology and reltively rare but have been associated with a host of inciting agents, from infections[4] to vaccines[5] to malignancies[6] and involve a multitude of immunological abnormalities.[7] The classification scheme popularized by Bohan *et al.*[8,9] and modified by Whitaker[4] appears in Table I. This review concentrates on types I, II, III and V.

Table I Clinical classification

Type I	Adult polymyositis
Type II	Dermatomyositis
Type III	Myositis with malignancy
Type IV	Childhood myositis
Type V	Myositis associated with other connective tissue diseases (Overlap syndrome)
Type VI	Miscellaneous: inclusion body, eosinophilic, and localized nodular myositis

Clinical manifestations

The clinical hallmark of PM/DM is weakness in the proximal muscles as well as in flexion of the neck and trunk. Patients usually notice lower extremity weakness first with difficulty rising from a squat or low chair or in climbing stairs. Upper extremity weakness follows with problems reaching above the head to comb the hair, hang clothes or reach cabinets. There is often noticeable sparing of both distal and facial muscles.[2] Dysphagia is present in 10–15% of patients[10] and predisposes to aspiration as well as being a marker for severe disease and a poor prognosis. One third of the patients show the unmistakable skin rash, with a purplish, dusky appearance, predominantly on the eyelids, cheeks and light-exposed areas. The rash may be patchy or confluent. It may also be seen on the extensor surface of the knees, elbows, knuckles and peri-ungally (Figure 1). Periorbital oedema is an important physical finding in the diagnosis of DM and may be seen in the absence of other skin lesions.

Calcinosis of subcutaneous tissues is a rare but dramatic complication. Widespread subcutaneous and muscle calcification, seen many years after the onset of PM, provide popular X-rays in examinations in the way of major disability. Some cases develop troublesome ulceration.

Another 5–10% of patients have pulmonary disease in the form of interstitial pulmonary fibrosis, respiratory muscle insufficiency or aspiration pneumonia.[11–13] Presentation of interstitial disease can be variable but patients frequently complain of fever, dyspnoea and non-productive cough, and there are usually basilar rales on physical examination. Findings on pulmonary function testing are those of a restrictive defect, reduced total lung capacity, limitation of diffusion and relative hypoemia.[2] The most common chest X-ray findings are those of a diffuse reticulonodular pattern. Histologically there is alveolitis, septal fibrosis, infiltration by lymphocytes and plasma cells, hyperplasia of type II pneumocytes and increased numbers of alveolar macrophages.[13] In a recent series from the Mayo Clinic pulmonary vasculitis was also seen frequently[14] although, in our own experience, pulmonary vasculitis is over-diagnosed. Like dysphagia, interstitial pulmonary disease seems

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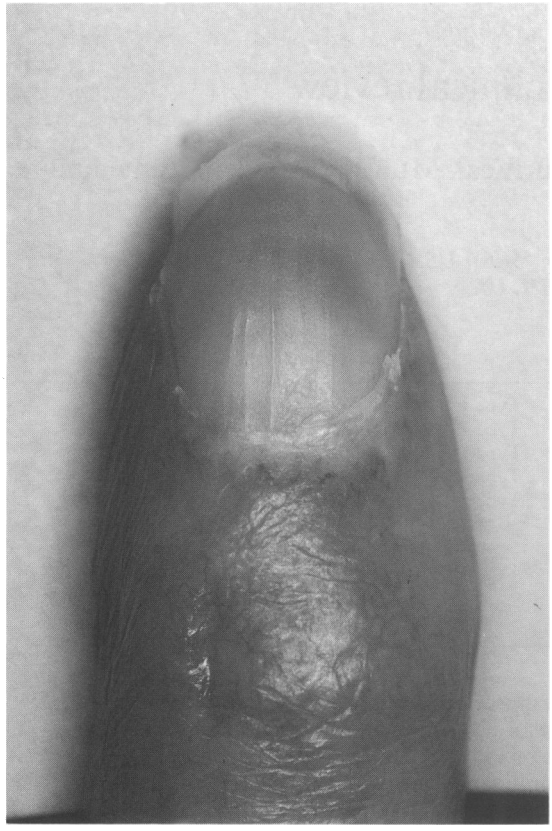

Figure 1 Periungal lesions in polymyositis.

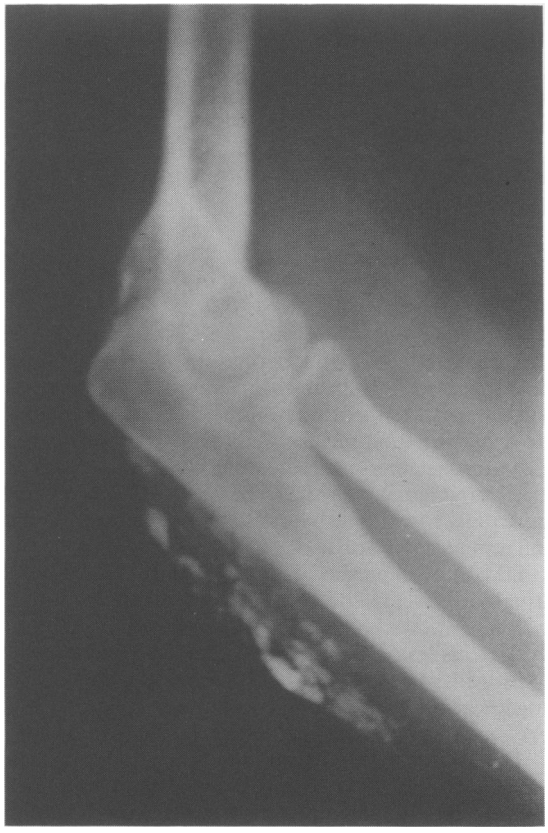

Figure 2 Widespread subcutaneous and muscle calcification in long standing polymyositis.

to be a poor prognostic feature. Rarely the pulmonary disorder precedes the muscle disease by months to years but when it follows the myositis it usually does so relatively early.[15]

Respiratory muscle weakness, on the other hand, usually becomes manifest at the same time as generalized muscle weakness and is frequently associated with pharyngeal dysfunction and aspiration[13] Tachypnoea, weak cough and radiographic evidence of atelectasis are clues to the diagnosis.

Aspiration pneumonia is the most common pulmonary complication in PM/DM, affecting as many as 14% of patients,[13] and is an important cause of mortality.[14] Almost all of these patients have high dysphagia with nasal regurgitation and a weakness of the pharyngeal and upper oesophageal muscles of deglutition. Fortunately, the interstitial fibrosis as well as the respiratory pharyngeal muscle weakness generally shows some response to corticosteroid therapy.[16]

Various types of cardiac conduction abnormalities have been described in PM. Fortunately, these are usually clinically silent.[17] In a large series, Bohan *et al.*[10] found arrhythmias in 6% of patients, bundle branch block in 5%, congestive heart failure in 3% and high grade block in 2%.

A local, nodular swelling in leg muscles is a rare variant in the presentation of PM, and when present usually precedes the generalized myopathy.[18] It may initially be clinically indistinguishable from a venous thrombosis.[19] Patients with myositis and overlap syndrome may display the whole spectrum of dermatological changes associated with connective tissue disease. Raynaud's syndrome occurs in one half of the patients with overlap syndrome as opposed to one fifth of those with more classical adult PM and DM.[20]

Muscular wasting is variable and frequently minimal until late in the disease. Contractures are almost exclusively associated with longstanding disease. Commonly arthralgias, without synovitis, are present in periods of active myositis.[21]

Laboratory findings

It is generally held that CK is the most sensitive laboratory indicator of disease activity in PM/DM[22] and although lactic dehydrogenase, aldolase and SGOT are also elevated, and are frequently measured, it is commonly felt that they are less reliable than CK.[23] A small percentage, 1–5%, of patients show no elevation of CK or of any other enzyme.[10] Conversely, the degree of CK elevation is a poor measure of the severity of the disease.[24] Even though the CK-MM isozyme always predominates there may actually be CK-MB present which is not felt to be of cardiac origin. Rather it is felt to come from regenerating skeletal muscle.[25] CK levels are followed, along with muscle strength, to determine response to therapy. There is a consistent, though imperfect, correlation between regained strength and falling CK. Recent technological advances have made it possible to measure muscle strength quantitatively, but unfortunately these biomechanical measurements do not correlate well with functioning ability or enzyme levels.[26]

Myoglobin, the respiratory protein of muscle cells, is released in massive amounts in PM/DM. Though not measured routinely, myoglobin levels, determined by radioimmunoassay, are in some ways a better measure of disease activity than CK.[27] However, if one is going to follow myoglobin levels they must be drawn at the same time of day because of diurnal variations.[28] Myoglobinuria may be associated (rarely) with renal failure in patients with PM/DM, as with other causes of rhabdomyolysis.[29]

In almost 80% of patients the EMG reveals low amplitude, short duration polyphasic potentials on voluntary contractions and fibrillation potentials at rest, all typical of myopathies.[27] Nearly 10% of patients though have a normal EMG, possibly because of a lack of sufficient sampling sites, given the multifocal nature of PM/DM. It is necessary, therefore, to sample both proximal and distal muscle groups as well as paraspinal muscles.[1] As an aside, it is also important to draw enzyme levels before the EMG is done in order to avoid spurious CK elevations from needle-induced trauma.

The gold standard for diagnosis is the muscle biopsy. It typically shows necrosis and regeneration of muscle fibres with infiltration of perivascular and interstitial spaces by small and large lymphocytes, macrophages and plasma cells (Figure 3).[31] If the disease process has been chronic, accumulation of lipid in conjunction with muscle atrophy are seen. As a matter of practical importance, the biopsy should not be taken from an area near EMG sampling since histological changes that are needle-induced may be misleading.

Muscle scintigraphy has been used to localize biopsy sites in PM as it demonstrates increased uptake of 99m-technetium-labelled phosphate in damaged muscles, presumably because of the increased binding of the phosphate to calcium in such muscles.[32] But, because this test is also positive in non-inflammatory myopathies and in trauma, its usefulness is limited in PM/DM outside of identifying appropriate muscles to biopsy. Fluorescein studies may provide the same information, as vascular permeability to fluorescein is increased in muscles with inflammatory changes.[33]

There is still debate as to which method of biopsy is best: open, needle or 'semi-open'. Each technique has its advantages. The open technique provides a large sample as well as overlying fascia, which is occasionally helpful in making the diagnosis, but

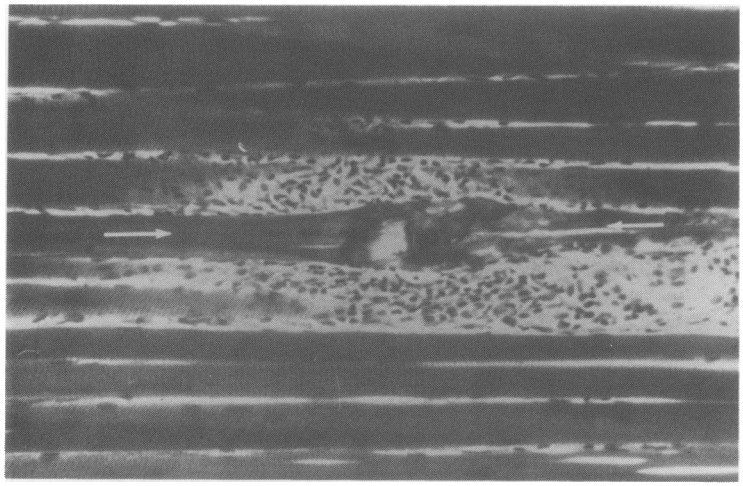

Figure 3 Muscle biopsy showing inflammatory cells and focal degeneration (arrows).

haematoma and infection are occasional complications. Needle biopsy can be done in numerous sites, increasing the diagnostic yield, but the specimen size is occasionally too small for the pathologist to make a confident diagnosis. The 'semi-open' technique is relatively non-traumatic and provides larger samples than the needle.[34] In general, the advent of needle biopsy has made life easier for physician and patient alike.

Diagnostic criteria

Unfortunately, many patients do not present with the classic findings. Often the clinical features are atypical, the enzyme patterns normal or equivocal and the EMG and biopsy merely suggestive. Here one may be helped by the criteria below, first published by Bohan and Peter[8,9] and more recently updated by Hodgrow and Peter.[35]

1. Predominantly or exclusively proximal, usually symmetrical, muscle weakness progressing over weeks or months with or without myalgia, with or without compatible dermatological features.
2. Biopsy evidence of muscle fibre necrosis, regeneration and mononuclear cellular infiltrate (perivascular and infrafascicular) with or without perifascicular atrophy.
3. Elevated serum CK levels (MM isozymes), aldolase or myoglobin.
4. Multifocal EMG changes of myopathy (small, short-duration, polyphasic motor unit potentials) with or without increased insertional activity and spontaneous potentials.

Satisfaction of all four criteria makes the diagnosis of PM/DM definite and the presence of three make it probable and justify beginning treatment, especially if the features of the first criteria are present and other toxic, infectious or metabolic causes are excluded.[1]

Immunological mechanisms

Both cellular and humoral processes are at work, but the exact mechanism of muscle injury remains unclear.[36] There is a close relationship between PM/DM and other autoimmune conditions, especially myasthenia gravis. Behan *et al.* had one remarkable patient who had PM, myasthenia gravis, Hashimoto's thyroiditis, pemphigoid, bladder carcinoma and Norwegian scabies.[37] Skin lesions in DM show histological and immunofluorescent changes almost identical to systemic lupus erythematosus with immunoglobulins deposited along the dermal-epidermal border.[38] Like many other immune disorders there is a predominance of HLA-B8 and DR3 in PM/DM, being present in 48% of patients with PM, 60% of patients with DM and only 31% of controls.[37]

Ninety percent of patients with PM have circulating antibodies to myosin[40] and numerous other antibodies have been found, directed at such diverse antigens as myoglobin, DNA, ribonucleoprotein (RNP)[40] and the extractable nuclear antigens PM-Scl, Mi, Ku and Jo-1[1,36] The latter has generated considerable interest since anti-Jo-1 antibodies seem to be not only a marker for PM but also for the subset of PM patients at risk for interstitial pulmonary disease.[41–44] The Jo-1 antigen is a subunit of histidyl transfer RNA synthetase.[45,46] Antibodies to RNP, on the other hand, are associated with mixed connective tissue disease[40,47] and antibodies to PM-Scl, with the PM-scleroderma antigen.[48] Anti-Ro and anti-SS-A antibodies are also sometimes seen in PM.[49]

The evidence for a cell-mediated mechanism is even stronger than that for a humoral. Lymphocytes from adults with PM/DM are cytotoxic to muscle cells in tissue cultures, apparently because of sensitization to muscle antigens.[4] This is not unlike the host-versus-graft response to muscle homografts. There is also activation of killer cells and the ratio of T-helper to T-suppressor cells is significantly elevated, in the range of 6:1 as opposed to the normal 2:1[37]

Furthermore, there is evidence of complement-mediated vascular injury at least in DM. The membrane $C_{5b\text{-}9}$ attack complex has recently been shown to be deposited and then activated within the intramuscular microvasculature with resultant vasculopathy.[50]

Despite the multiple derangements of the immune system in DM the mechanism for these derangements has continued to elude investigators.

Association with infection

There have been sporadic reports of PM/DM developing in association with vaccination[5] or a viral illness especially with Coxsackie viruses[51,52] and human immunodeficiency virus.[53,54] There is also an association with recent toxoplasmosis infections,[55] but the question arises whether the toxoplasmosis caused PM or whether the PM, by virtue of its immunosuppressive nature, allowed for reactivation of latent toxoplasmosis, or other infections for that matter.

Association with malignancy

For over half a century there has been debate over the association of PM/DM with an occult malignancy. Despite multiple studies in the literature an exact relationship has never been established. Physicians have tended, nevertheless, to put their patients with a

new diagnosis of PM/DM through extensive evaluations for occult malignancy. Recent studies have failed to demonstrate a clear association.[6,56] A Mayo clinic series showed a slightly increased incidence of cancer in PM/DM patients but it was not statistically significant and seemed to be explained on the basis of referral bias.[6] PM/DM had previously been linked to oat cell carcinoma of the lung, stomach and ovarian cancer and numerous other malignancies.[57] A recent Canadian study found multiple methodological problems with previous studies showing these associations and although they found a higher frequency of neoplasms in PM/DM than in controls, these malignancies were found to be present at entry in the study and no statistically significant increase in subsequently diagnosed malignancy was ever found.[56] The question of association with malignancy must still be considered unanswered as is the dilemma of how extensive a 'cancer work-up' these patients should receive. Recent authors recommend a thorough history and physical examination as well as complete blood counts, multiphasic biochemical analysis of the blood, urinalysis, stool guaiac test and chest radiograph.[58,59] Further diagnostic tests should be directed by any abnormalities in these general screening tests.

Therapy

Before therapy is begun it is of utmost importance for the diagnosis to be accurate, the activity of the myositis assessed and the patient prepared for a somewhat long and, at its outset, frustrating therapeutic regimen. The latter includes physical therapy in periods of remission and rest periods in active myositis. Oral corticosteroids, in the form of prednisone in doses of 40–60 mg/day (1 mg/kg/day), is the backbone in the initiation therapy.[2] This dose is continued for 1–2 months or until maximum benefit or disease remission is attained. The decision of when to begin tapering is usually made when improvement in muscle strength is seen and CK levels are declining. An important rule is that tapering must be slow. Mastaglia and Ojeda[1] recommend a reduction in the daily dose of 5 mg every week until reaching 30 mg/day and then reducing it by 2.5 mg a week until a dose is reached which maintains muscle strength and low enzyme levels though this may be excessively slow. The usual cause of relapse after a good initial response is too early or too precipitous a reduction in dosage. CK levels may be helpful in avoiding this. They tend to begin their rise several weeks before a clinically observable relapse[9] so careful monitoring of the CK levels after making a dosage reduction is appropriate. Some patients, especially those with mild disease, may be able to maintain their remission with fewer steroid side effects on an alternate day regimen.[60] Patients who develop steroid-induced myopathy may be distinguished from those with reactivated PM/DM by repeated CK, EMG and biopsy studies, all of which should show continued improvement and response to therapy if the myopathy is due to steroids.

Patients not responding to glucocorticoids or who are intolerant of their side effects may be treated with immunosuppressants – methotrexate, cyclophosphamide (including pulse intravenous cyclophosphamide), chlorambucil and azathioprine being the most commonly used.[2,10,61,62] Indeed many now advocate combined steroid and immunosuppressive treatment from an early stage. Rare patients unresponsive to all these treatments may be helped by plasmapheresis[63] or total body irradiation.[64–66]

Prognosis

Five year mortality in PM/DM in numerous published series has ranged between 13.7% and 50%.[10,67] An actuarial study from Israel[68] identified the following as independent unfavourable prognostic signs in PM/DM: failure to induce remission, leucocytosis over 10,000/μl, fever over 38°C, older age, a short disease history and dysphagia. The common denominator in a number of these risk factors was the development of aspiration pneumonia. Other factors, long thought to be signs of poor outcome, such as the presence of another autoimmune disease or of malignancy, duration and severity of PM/DM, degree of enzyme elevation or cardiac manifestations were not shown to be significant.[68]

Conclusion

Many questions remain unanswered in PM/DM. For the epidemiologist there is the problem of risk groups and inciting agents. For the immunologist there is the dissection of the exact mechanisms of immune injury. For the neurophysiologists there is the challenge of better non-invasive testing both for diagnosis and evaluation of response to therapy, and for the clinician there are concerns about how extensively to look for cancer and how to treat. There is no consensus about the optimal starting dose of prednisone, the timing and manner of dose reduction, the length of therapy in 'responders', the best means of evaluating response, the role of pulsed methylprednisolone, the characteristics of 'steroid resistance' or the most appropriate use of immunosuppressants and other interventions.

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